High-Risk, Clinically Localized Prostate Cancer: Is Monotherapy Adequate?

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High-risk, clinically localized prostate cancer represents a diverse disease entity. Patients who are considered to be at highest risk for biochemical failure after localized treatments may not be at significant risk for disease-specific mortality. In this review, an attempt will be made to define high-risk status and help identify patients at high risk for mortality after a diagnosis of localized prostate cancer. Subsequently, a review of monotherapy approaches as well as previously successful strategies utilizing multimodality therapy for high-risk disease will be presented. Finally, a synopsis will be given of several ongoing randomized clinical trials using the most effective systemic therapies in the adjuvant setting following thorough local treatments such as radical prostatectomy. This review will provide a glimpse into the future and describe the tools that it is hoped will improve further upon the results of surgical monotherapy for high-risk, localized prostate cancer.
[Rev Urol. *2007;9(suppl 2):S19-S27*]

Key words: Prostate cancer • High-risk, localized prostate cancer • Mortality risk • Multimodality therapy • Radical prostatectomy

The increasing median age of the American population and a steadily increasing life expectancy will force a new-found focus onto the treatment and long-term outcome of all age-related malignancies. Adenocarcinoma of the prostate offers a classic example of an age-related malignancy that will be more commonly encountered as the "baby boom" generation ages. Despite the well-described downward stage migration encountered in the era of prostate-specific antigen (PSA), there still exists a subset of patients with prostate cancer diagnosed with what has loosely been described as high-risk, localized prostate cancer. The goals of this article are (1) to further characterize this patient population by

defining high-risk, localized prostate cancer, (2) to review the treatment modalities that are currently available for this patient population, (3) to discuss the reported outcomes of the different treatment options, and (4) to elucidate the ongoing randomized clinical trials addressing high-risk, localized prostate cancer. Particular attention will be paid to the success of multimodality therapies when compared with single-agent therapies.

Defining High-Risk Prostate Cancer

It is of the utmost importance to clearly define the patient population being considered as having high-risk, localized prostate cancer before embarking on an analysis of their treatment options. Patients with any cancer must be considered at high risk for arriving at one of a number of specific endpoints. There are a multitude of different endpoints that can be analyzed, such as clinical relapse, treatment-related complications, the development of second primary malignancies, and, ultimately, death from cancer. In the case of prostate cancer, the most commonly discussed endpoint is biochemical or PSA-only recurrence. Biochemical recurrence (BR) is actually experienced by up to 35% of all patients with localized prostate cancer, and in the vast majority of these individuals, no actual morbidity or mortality is experienced. In the sentinel work on this topic, Pound and colleagues from Johns Hopkins[1] reported that of the 1997 men treated surgically for prostate cancer at their institution, 315 (15%) experienced BR, and of these only 103 (34%) went on to develop metastases. This indolent natural history of BR helps us shape our understanding of how we should define high-risk, localized prostate cancer. Patients with high-risk, localized prostate cancer should be those who are considered at high risk of experiencing either death from prostate cancer or the development of clinical metastases. In fact, during the recent 2005 Conference on Innovations and Challenges in Prostate Cancer, high risk was defined as "significant likelihood of progressive, symptomatic disease or death from prostate cancer."[2] Multimodality therapy to reduce the risk of biochemical-only recurrence cannot be considered rational. BR is not an illness with any symptoms, and a large proportion of patients experiencing BR are not destined to progress or succumb to prostate cancer. It is only when examined in this context that the principle of multimodality therapy is thoughtfully reviewed.

The most commonly discussed endpoint of prostate cancer is biochemical or prostate-specific antigen-only recurrence.

Risk Stratification Techniques

Throughout the past 15 years, the process of predicting individual prostate cancer patient outcomes has evolved from anecdotal-based guesswork into a precision, evidence-based scientific algorithm. This rapid evolution has been aided by rigorous retrospective statistical modeling and the ever-increasing processing capability of the personal computer. This field has been led by the breakthrough vision of several pioneers such as Kattan from the Cleveland Clinic, Partin from Johns Hopkins, and D'Amico from Harvard University.[3,4] With the use of their respective risk stratification models, clinicians can with great accuracy identify patients with prostate cancer who are at high risk for either adverse pathologic outcomes or BR.

The continuous variable method of Kattan and colleagues,[3] originally described in 1997 and often referred to as a nomogram, allows for the greatest individualization of risk and the most accurate prediction of outcomes. This technique does not require grouping of large numbers of dissimilar patients into single-risk groups. On the contrary, the method originally described by D'Amico and colleagues[4] separates patients into low-, intermediate-, and high-risk groups. Regardless of the method chosen, each technique allows prediction of risk for BR. However, as stated previously, this does not equate into a high risk of death from prostate cancer. Because one cannot translate the risk of BR into the risk of death, it is difficult to determine how low a nomogram score a patient must have to be identified as high-risk for prostate cancer–specific mortality. Recently, we reviewed our institutional experience with all patients treated by radical prostatectomy with a postoperative Kattan risk-stratification score of less than 60%. The majority of the patients did, in fact, experience BR. However, 95% were alive at an estimated follow-up of 15 years without the use of multimodality therapy during their original treatment.[5] Kattan and colleagues[3] have more recently attempted to refine their predictive tool to enable prediction of clinical metastases following radiation therapy. This is a helpful adjunct in the identification of high-risk patients. However, the ultimate model to predict risk of death from prostate cancer will be difficult to develop because this endpoint is infrequently achieved and often takes a long time following initial therapy for localized disease.

In an effort to better define a high risk of death from localized prostate cancer, D'Amico and colleagues[4] have now presented compelling data for the incorporation of PSA velocity

(PSAV) as a surrogate for death from prostate cancer into our decision-making process. Their group has demonstrated that patients exhibiting a rapid PSAV either before radical prostatectomy or at the time of BR are at an independently increased risk of dying from prostate cancer when controlling for stage, grade, and total PSA at diagnosis. Another study by Freedland and colleagues from Johns Hopkins followed 379 men with BR after radical prostatectomy.[6] They found that a PSA doubling time (PSADT) of less than 3 months predicted a high risk of dying from prostate cancer. In addition, Gleason score (7 vs 8-10) and time from surgery to BR were also significant risk factors for time to prostate cancer–specific mortality.[6] It appears that using the kinetics of PSA recurrence (PSAV and PSADT) represents the most practical and readily available method to help identify which patients at high risk for BR are, in fact, at high risk for death from their disease and, therefore, should be incorporated into the design of clinical trials as well as the day-to-day decision making in the management of high-risk, localized prostate cancer. Unfortunately, throughout the subsequent analysis of the available literature, the definition of high risk in each treatment series will vary and will be based largely on the estimated risk of BR rather than the risk of prostate cancer–specific mortality.

A prostate-specific antigen doubling time of less than 3 months predicted a high risk of dying from prostate cancer.

Results of Monotherapy

Surgery

When analyzing the utility of multimodality therapy for high-risk, localized prostate cancer and determining if, in fact, it represents a significant improvement over monotherapy, one must first come to an understanding of the expected outcomes following monotherapy with each available modality. In the absence of a well-designed and completed randomized clinical trial, this must be accomplished by a comparison of separate retrospective series. When discussing surgical monotherapy for high-risk, localized prostate cancer, there exist several retrospective series with variable reported rates of outcomes. One must, however, remember that the investigators' definitions of high-risk, localized prostate cancer vary from study to study. Lau and colleagues[7] from the Mayo Clinic have reported on their observed outcomes with 407 high-risk, localized prostate cancer patients following surgery alone. They defined high-risk patients solely by their Gleason score ranging from 8 to 10 on the final pathologic specimen. With this in mind, they found that 23% of their patients who received no adjuvant therapy were alive without evidence of disease at 10-year follow-up. Conversely, more than 75% of their patients treated with surgery alone had relapsed. In a higher-risk population of patients with regional metastases at the time of surgery, Messing and colleagues[8] demonstrated the risk of prostate cancer-specific mortality when surgery is applied as monotherapy. In their randomized clinical trial, 31% of men treated by radical prostatectomy alone died of prostate cancer after 7 years. Obviously, this cohort of men with nodal metastases on final pathology represents the highest-risk population of patients with clinically localized disease at the time of surgery. The data from Messing and colleagues,[8] however, can be used to demonstrate that high-risk patients indeed, have a risk of relapsing that is not addressed solely by treatment of their primary tumor surgically. These observations are useful in counseling patients regarding the role of surgical monotherapy for high-risk, localized prostate cancer. Although not impossible, it is rare to achieve long-term freedom from disease recurrence by utilizing surgical monotherapy.[8]

The investigators' definitions of high-risk, localized prostate cancer vary from study to study.

The topic of surgical therapy for high-risk prostate cancer does merit some discussion about current practice trends. Often patients with high-risk features are counseled that they are not candidates for surgical therapy and are advised to undergo less invasive treatments such as radiation therapy. Ironically, most clinicians will describe surgical therapy as the most effective means of controlling intermediate- and low-risk disease in young men. Why, then, should the more effective primary therapy be denied to a patient with high-risk disease who, in fact, has the highest risk of dying from prostate cancer? This notion is counterintuitive and is not seen in most other epithelial malignancies such as breast and colorectal cancers. With the improvements in surgical morbidity and the reduction of perioperative surgical mortality to nearly undetectable levels, it certainly seems logical to reevaluate the rationale for not operating on high-risk patients simply because they are unlikely to be cured by surgery alone. As a starting point for multimodality

therapy, it is likely, although unproven, that surgical removal of the primary organ provides the highest likelihood of response to any adjuvant therapy, whether it is androgen deprivation, radiation, or chemotherapy.

Radiation Therapy

Perhaps the most contemporary way of analyzing external-beam monotherapy for high-risk, localized prostate cancer is to examine the control arm of one of the most commonly referenced randomized clinical trials in radiation oncology. Bolla and colleagues[9] randomized 415 patients with clinically localized high-risk or locally advanced prostate cancer to either external-beam radiation therapy (EBRT) alone (n = 208) or EBRT plus a luteinizing hormone-releasing hormone analogue for 3 years (n = 207). They defined high-risk patients as those with T1-T2 disease and World Health Organization grade 3 histology in the absence of lymph node metastases, or T3-T4 disease of any histologic grade without nodal metastases. At a median follow-up of 45 months, Kaplan-Meier estimated that 5-year overall survival and disease-free survival for the EBRT-only group were 62% and 48%, respectively. A subsequent analysis of this trial published in 2002 with 66 months follow-up demonstrated for the EBRT-only arm an overall survival and disease-free survival of 62% and 40%, respectively.[10]

Owing to a paucity of randomized clinical trials, there have been numerous retrospective series assessing the efficacy of radiation therapy alone for high-risk, localized prostate cancer. The most recent study published by Tewari and colleagues[11] defined high-risk, clinically localized prostate cancer as Gleason > 8 on the biopsy pathology. Four hundred fifty-three patients were treated with either observation, radiation therapy, or radical prostatectomy. Median cancer-specific survival was greater than 14 years for both the radiation therapy and surgery cohorts. Again, it is important to remember that the definition of high-risk, localized prostate cancer is highly variable from study to study, making a direct comparison among different series impossible. Nonetheless, similar to the results with surgical monotherapy, radiation therapy alone is unlikely to yield long-term, disease-free survival in patients with high-risk, localized prostate cancer.

Androgen Deprivation Therapy

Most monotherapy strategies consist of localized treatment such as surgery or radiation therapy. The use of systemic monotherapy in the form of androgen deprivation therapy (ADT) has been recently reanalyzed. There exist very little data in this subset of patients with high-risk, localized prostate cancer to allow meaningful conclusions to be drawn. However, the Japanese group led by Akaza[12] recently reported on the 10-year survival rates for men with localized or locally advanced prostate cancer treated with primary ADT. One hundred fifty-one men with T1-3N0M0 prostate cancer were treated with ADT alone. With a median of 10.4 years of follow-up, they observed a 10-year overall survival rate of 41% and a disease-specific survival rate of 78%. Although the previous study did not strictly focus on high-risk, localized disease, the results indicate that in a heterogeneous population of men, reasonable cancer-specific survival rates can be achieved with ADT monotherapy. In a subset analysis, Akaza and colleagues[12] defined high-risk patients as those with T2b, poorly differentiated cancer, or an initial PSA of > 20 ng/mL. They defined a "very high-risk" group as those patients with T3 disease. Ten-year cancer-specific survivals in the high-risk and very high-risk patients were 91% and 69%, respectively.[12] Thus, even in a high-risk subset of patients, ADT monotherapy achieved respectable cause-specific survival rates at 10 years' follow-up. Of note, the average age of the patients in this study was 76 years, making it less likely for subjects to die of their disease over the ensuing 10 years. In addition, the long-term morbidity of continuous ADT for 10 years is a significant consideration that was not addressed in the above study. Perhaps intermittent ADT monotherapy also deserves investigation for high-risk, localized prostate cancer given its lower morbidity than continuous ADT.[12]

Multimodality Therapy

Surgery Followed by Radiation Therapy

The combination of 2 localized therapies to combat high-risk, localized prostate cancer has always seemed to provide a rational solution to high-risk disease. However, the propensity for distant failure in patients with features such as seminal vesicle involvement as well as positive lymph nodes has limited the utility of combined localized therapy in the highest-risk patients. Innumerable retrospective single-institution series have reported on their own experience with postoperative radiation therapy in both the adjuvant setting and the salvage setting. For the purposes of defining these treatments, adjuvant radiation is given following surgery when the patient's PSA is undetectable. Salvage radiation therapy, however, is defined as radiation given in the setting of a rising PSA or with evidence of clinical metastases.

A randomized clinical trial by Thompson and colleagues[13] evaluated the potential benefit of adjuvant radiotherapy after radical prostatectomy for high-risk patients with T3N0M0 disease. Four hundred twenty-five men were randomized to

adjuvant EBRT or usual postoperative care plus observation. Patients within each arm of the trial demonstrated high-risk features but were not required to have a positive surgical margin. Because the study was designed before the PSA era, an undetectable PSA was not required. This study revealed a 47% chance of freedom from PSA recurrence at the 10-year mark in the treatment arm versus a 23% chance in the observation arm. However, this advantage did not translate into a significant improvement in disease-specific survival.

EORTC 22911 is another large randomized clinical trial that assessed the effect of adjuvant radiation therapy after radical prostatectomy for high-risk, localized prostate cancer.[14] Eligible patients had either capsular penetration of disease, positive surgical margins, or seminal vesicle invasion. Patients with lymph node metastases were excluded. One thousand five patients who underwent radical prostatectomy were randomized to either observation or immediate EBRT. At a median follow-up of 5 years, the radiation group demonstrated a significant improvement in biochemical progression-free survival (74% vs 52.6%) and a decrease in locoregional failure. Overall survival, after a relatively short follow-up period, was not statistically different between the 2 groups.

The previous studies are examples of how multimodality therapy can decrease the incidence of BR without improving clinically significant outcomes such as progression to metastases or survival.

There are several retrospective, single-institution series also examining the potential benefit of postoperative radiation therapy (Table 1).[14-16] Each individual series would indicate that postoperative radiation therapy is best administered when the PSA is less than 1.0 ng/mL and, perhaps, ideally when it is undetectable. When administered in this fashion, virtually all series have identified a substantial advantage in freedom from PSA progression. However, no trial to date has demonstrated a survival advantage associated with this combination therapy. Several factors have been identified that increase a patient's likelihood from benefiting from postoperative radiation, including Gleason score less than 7, more than 2 years between surgery and biochemical failure, and the presence of positive surgical margins.

Table 1
Biochemical Progression-Free Survival Following Adjuvant Radiation Therapy

Study	Adjuvant EBRT (%)	Control (%)	Overall Survival
Bolla et al, EORTC 22911[14]	74	53	NS
Leibovich et al, Mayo Clinic[15]	88	59	NS
Stein et al, UCLA[16]	75	43	NS

EBRT, external beam radiation therapy. NS, not statistically different.

Radiation Therapy Plus Androgen Deprivation

Perhaps the most well described and most frequently used multimodality regimen in the urologic community is radiation therapy plus concomitant ADT for high-risk, clinically localized prostate cancer patients. The rationale for this combined approach is that the radiation controls the primary tumor, whereas concomitant systemic ADT eradicates locally advanced and micrometastatic disease. The randomized clinical trial by Bolla and colleagues[9,10] discussed previously is the paradigm for randomized controlled trials comparing EBRT alone versus EBRT plus immediate ADT for high-risk, localized and locally advanced prostate cancer. Again, 415 high-risk patients were randomized to the above 2 arms of the trial. ADT was started at the inception of the radiation therapy and continued for 3 years in the combined modality group. At a median follow-up of 66 months, 5-year disease-free survival was 40% and 74% in the radiotherapy-alone and combined treatment groups, respectively ($P = .0001$). Five-year overall survival was 62% and 78%, respectively ($P = .0002$) (Figure 1). These results provided strong evidence that immediate multimodality therapy (EBRT + ADT) was better than EBRT alone. Of note, without an ADT-only arm in the trial, it is difficult to make any conclusions about the relative contributions of ADT and EBRT to the improved outcomes. In other words, could ADT-alone have yielded similar results to the ADT + EBRT treatment arm?

Surgery Plus Adjuvant Androgen Deprivation Therapy

Surgery plus adjuvant ADT has also been investigated as a potential treatment option for high-risk, localized prostate cancer. The landmark randomized trial by Messing and colleagues[8] in 1999 examined high-risk patients who all underwent radical prostatectomy and bilateral pelvic lymphadenectomy and were found to have lymph node metastases. Ninety-eight patients were randomized to immediate ADT or observation until clinical

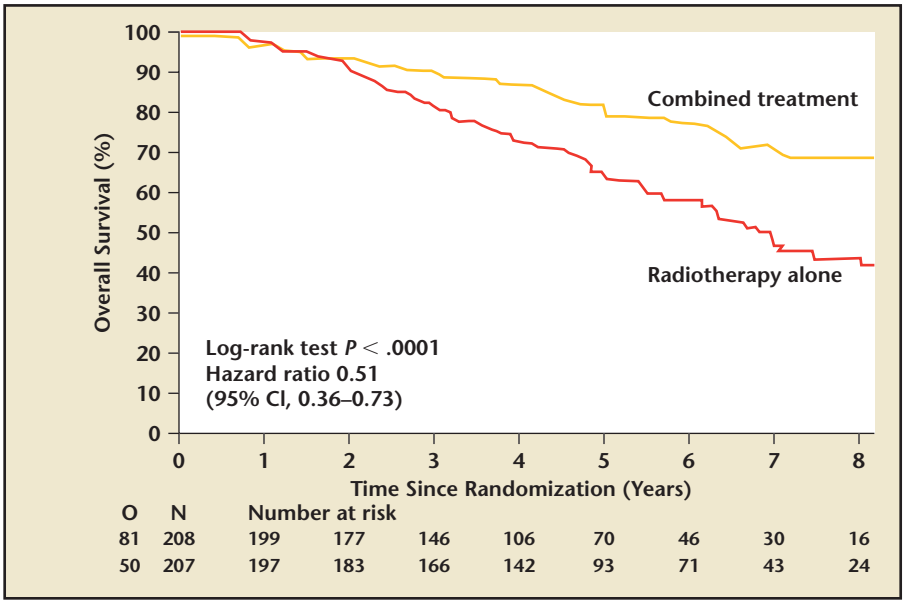


Figure 1. *Results of EORTC 22863: Overall survival at 5-year follow-up. O, number of deaths; N, number of patients. Reprinted with permission from Bolla M et al.*[10]

progression of disease. At a median follow-up of 7.1 years, only 7 of the 47 men in the immediate ADT group versus 18 of the 51 men in the observation group had died ($P = .02$). In addition, only 3 men in the ADT arm died of prostate cancer compared with 16 in the observation cohort. Seventy-seven percent of the patients in the ADT group and 18% of those in the observation group were alive and without evidence of disease at the last follow-up (Figure 2). The results from this, albeit small, randomized trial clearly support the practice of surgery plus immediate ADT compared with surgery and observation for this very-high-risk subset of patients with nodal metastases.

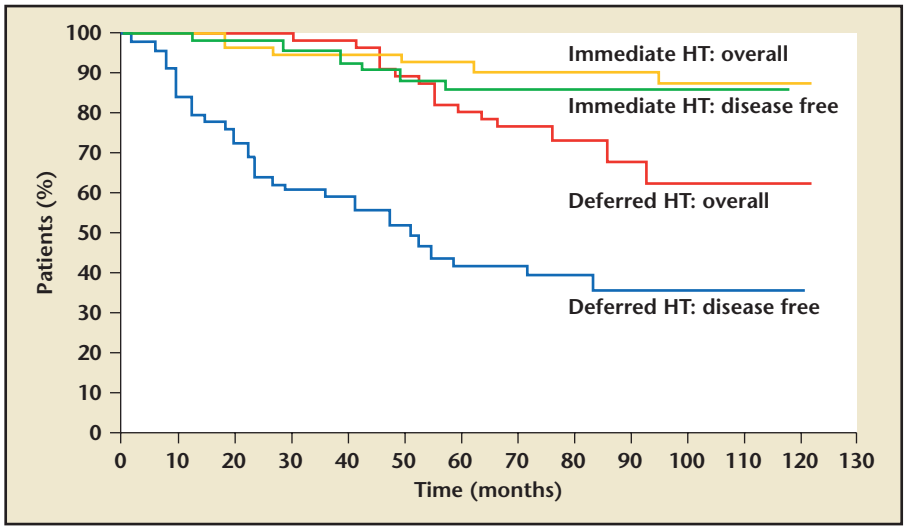
Messing and colleagues published an update to the previous randomized trial in 2006.[17] With a median follow-up of 11.9 years, the men who received immediate adjuvant ADT still demonstrated a significantly improved overall survival, disease-specific survival, and progression-free survival compared with those who received delayed ADT upon progression.

Localized Therapy in Combination With Chemotherapy

The advent of effective systemic cytotoxic chemotherapy for hormone-refractory prostate cancer has led to the application of taxane-based chemotherapy as an adjunct to definitive local therapy in many recent clinical trials for high-risk prostate cancer.[18] Kumar and colleagues[19] published a thoroughly designed phase I clinical trial to test the feasibility of EBRT in conjunction with weekly docetaxel-based chemotherapy. Patients with high-risk, localized prostate cancer underwent daily three-dimensional therapy to a total dose of 70.2 Gy at 1.8 Gy/fraction and concurrent docetaxel given once a week for 8 to 9 weeks. Docetaxel doses were escalated as follows: 8, 12, 16, 20, and 25 mg/m^2. Eventually 22 men completed the chemoradiation therapy protocol. The dose-limiting toxicity was grade 3 diarrhea, which occurred in the first 2 patients treated at the 25-mg/m^2 docetaxel dose level. Seventeen patients remained free from PSA progression after a relatively short-term median follow-up of 8 months (range, 2-27 months).

This strategy was also applied by Hussain and colleagues[20] in the neoadjuvant setting. They defined high-risk, localized prostate cancer as patients with either clinical stage T2b

Figure 2. *Survival results of ECOG 7887. HT, hormonal therapy. Adapted from Messing EM et al.*[8]



or greater or PSA of 15 or greater, or Gleason score of 8-10. Chemotherapy consisted of docetaxel (70 mg/m^2) on day 1 and estramustine (280 mg 3 times daily) on days 1 to 3 every 21 days for 3 to 6 courses. This was followed by local therapy in the form of either radical surgery or radiation therapy. Twenty-one patients with a median age of 60 years and median PSA level of 16.1 ng/mL (range, 2.4-175 ng/mL) were enrolled. A median of 5 cycles of chemotherapy was delivered. The most frequent high-grade toxicities were grade 3 (8 patients) and 4 (1 patient) neutropenia and deep venous thrombosis. Ten patients underwent radical prostatectomy, with negative surgical margins in 7 patients, and 11 received radiotherapy with negative preradiotherapy biopsies in 2. These 2 studies taken in concert revealed the feasibility of early stage taxane-based therapy in the multimodality therapy of high-risk, localized prostate cancer.[19,20]

These early studies have led to a recent completion of a nonrandomized phase II trial using adjuvant docetaxel in patients at high risk for recurrence after radical prostatectomy. Patients were deemed high risk if they demonstrated a greater than 50% risk of relapse in 3 years. Docetaxel 35 mg/m^2 was given at days 1, 8, and 15 of a 28-day cycle for 6 cycles starting 4 to 12 weeks following surgery. A total of 77 patients were treated with pathology demonstrating positive seminal vesicles in 50/77 (65%), positive lymph nodes in 22/77 (29%), and positive margins in 50/77 (65%). The Gleason score was 7, 8, 9, and 10 in 44%, 13%, 39%, and 3% of patients, respectively. At median follow-up of 28 months, 47 of 75 evaluable patients (63%) progressed. Median progression-free survival (PFS) was 16.3 months (95% CI, 13.0-19.8 months). Predicted PFS was 10.0 months. Seven patients died; 4 from prostate cancer. Grade 3 toxicity occurred in 20 (26%) of the patients and included hyperglycemia, dyspnea, cardiac arrhythmias, and pulmonary fibrosis. Grade 4 toxicity was hyperglycemia in 2 patients that resolved, and a gastrointestinal bleed resulting in death in 1 patient that was possibly related to treatment. This study demonstrated that use of adjuvant docetaxel may be possible—however, with significant toxicity in a population of patients with high-risk, localized prostate cancer.[21]

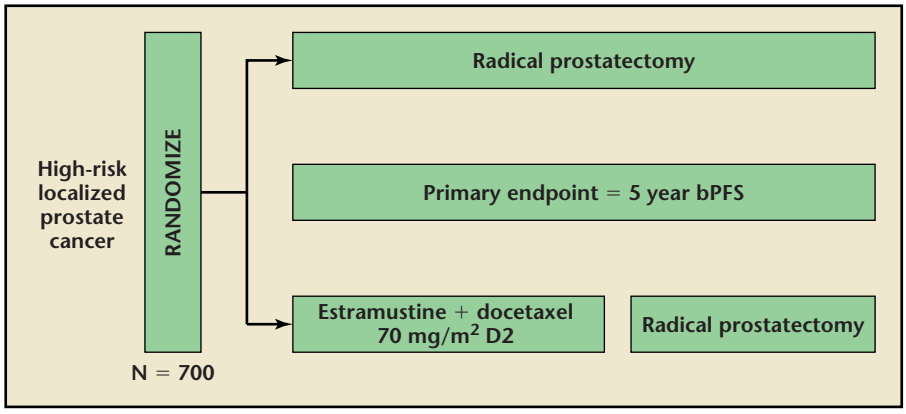
Future Promise

Neoadjuvant Docetaxel Therapy

A recently initiated randomized clinical trial within the Cancer and Leukemia Group B (CALGB) is attempting to address the efficacy of neoadjuvant docetaxel-based therapy in 700 patients with high-risk, localized prostate cancer. This trial,[22] titled CALGB 90203 trial, will be led by James Eastham, MD, a urologist, and will define high-risk, localized prostate cancer as a predicted probability of less than 60% of remaining free from disease recurrence for 5 years after surgery as defined by the Kattan nomogram. Patients with a greater than 10-year life expectancy will be randomized to either radical prostatectomy alone or estramustine and docetaxel before radical prostatectomy (RP) (Figure 3).

Eligible patients will be stratified according to their predicted probability of remaining free from disease recurrence at 5 years after surgery (0% to 20%, 21% to 40%, and 41% to 60%) and then randomized. Neoadjuvant chemotherapy will be administered in 6 cycles (1 cycle = 21 days) of estramustine (280 mg 3 times daily, days 1 to 5) and docetaxel (70 mg/m^2 on day 2). Bilateral pelvic lymph node dissection and RP will then be performed. Biochemical disease recurrence will be defined as a serum PSA level greater than 0.4 ng/mL on 2 consecutive occasions 3 or more months apart after RP. The primary endpoint is to determine if early systemic treatment with neoadjuvant estramustine and docetaxel before RP in patients with high-risk prostate cancer will decrease 5-year recurrence rates when compared with RP alone as measured by PSA progression. Secondary outcomes will include the safety and tolerability of the regimen, and the impact of this neoadjuvant strategy on pathologic tumor stage, including lymph node and surgical margin status as well as overall survival. Furthermore, using high throughput DNA array–based methods of expression analysis, the sensitivity to chemotherapeutic agents and response to chemotherapy may be

Figure 3. *Study design of CALBG 90203. Phase III study of radical prostatectomy alone versus neoadjuvant docetaxel plus estramustine in high-risk, localized prostate cancer. bPFS, biochemical progression-free survival rate.*



predicted for better selection of high-risk patients in the future.[22]

Adjuvant Docetaxel Therapy

The most promising ongoing adjuvant chemotherapy trial in high-risk prostate cancer is the adjuvant docetaxel study involving the use of immediate postoperative docetaxel versus observation in patients with high-risk, localized prostate cancer. This trial is due to accrue 1696 patients in the next several years. The trial has a unique design that will call for a second randomization at PSA recurrence for those patients in the observation arm. This trial will serve as the ultimate benchmark to determine if perioperative docetaxel-based chemotherapy will ultimately be capable of benefiting men with high-risk, localized prostate cancer who have undergone definitive surgical intervention.

This clinical trial will potentially determine 2 different things. First, can immediate adjuvant docetaxel decrease the risk of mortality in a high-risk population? Second, can this decrease in risk be achieved even if the intervention is withheld until the time of PSA relapse?

Conclusions

When an accurate definition of high-risk, localized prostate cancer is applied, monotherapy with either surgery or radiation therapy is probably not adequate treatment. It is also clear that most definitions of high-risk, localized prostate cancer do not describe patients at high risk for death but rather high risk for biochemical recurrence. The small subpopulation of patients with localized prostate cancer that is at significant risk of disease-specific mortality have benefited in each example of a strategy that adopted a multimodality approach. This patient population will likely benefit more in the future from the introduction of more forward-looking strategies that combine effective local therapy with more effective adjuvant systemic therapies.

The most promising ongoing adjuvant chemotherapy trial in high-risk prostate cancer is the adjuvant docetaxel study involving the use of immediate postoperative docetaxel versus observation in patients with high-risk, localized prostate cancer.

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Main Points

- Patients with localized prostate cancer considered at highest risk for biochemical failure after localized treatments may not be at significant risk for disease-specific mortality; high-risk status needs clarification to identify patients at high risk for mortality.
- With the use of risk stratification models, clinicians can with great accuracy identify prostate cancer patients who are at high risk for either adverse pathologic outcomes or biochemical recurrence.
- Monotherapy may not be adequate treatment when high-risk, localized prostate cancer is diagnosed and defined.
- Multimodality therapy can decrease the incidence of biochemical recurrence and in several clinical trials has demonstrated a survival advantage.
- This high-risk patient population will likely benefit from strategies that combine effective local therapy with more effective adjuvant systemic therapies.

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